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$PM_{2.5}$, $PM_{2.5}$-related air pollutants, health hazards and impacts on respiratory and cardiovascular disorders and diseases: systematic review and meta-analysis

Abstract

The objective of the study is to perform a critical review, exploration, and strong summary of the relationships between personal and ambient concentrations of mainly particulate matter with diameter of 2.5µm or less with the measures of cardiopulmonary health. A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including Scien Direct, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between 2017 and early 2019. Needed article information was extracted from each article by: direct information including journal (research article, review article, meeting abstract, conference abstract, correspondence, author index, editorial board meeting abstract, discussion), book chapter, title, authors, abstract, full text documents of candidate studies, publishing year. Study period, Research (study) method used, types of air pollutants variables studied; Types of organ system disorder or disease studied The conclusions made about the health hazards, impacts on humans or animal models, novel therapeutics, and economic loss.

With strict literature search and screening processes, it yielded 140 articles (2017=45; 2018=61; and early 2019=34 articles) from 3,968 articles of initial literature database (1952-early 2019). The main compositions of air pollutants are PM, particularly $PM_{2.5}$ and PM_{10}, O_3, CO, SO_2, and NO_x. Exposure to O_3 is frequently associated with respiratory tract inflammation, whereas exposure to PM, CO, No_2, and SO_2 is related to pulmonary edema, respiratory and cardiovascular hospitalizations, and cardiopulmonary mortality. Any compromise to endothelial cells, the key components of lung barrier integrity contributes to vascular leakage and inflammation. Endothelial cells could be the target of PM exposure. The various effects on various disease entities contribute to hypothesize that Melatonin might protect the lung integrity against $PM_{2.5}$-induced acute lung injury. Bufei Huoxue (BFHX) could reduce secretory immunoglobulin A (sIgA) and collagen fibers deposition in lung, thus, improved pulmonary function. In conclusion, identification of various crucial signaling pathway involving PM-induced cardiopulmonary disorders and diseases may assist in the development of effective therapeutics, including clean energy use, clean industrialization, proper agriculture, high land use diversity, and proper urbanization for reduction of the air pollution.

Keywords: $PM_{2.5}$, respiratory, cardiovascular, cardiopulmonary, disorders, diseases, health, impacts, hazards

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Abbreviations: ACLY, adenosine triphosphate citrate lyase; Au, gold; Al, aluminum; AP, attributable Proportion; As, arsenic; ATP, adenosine triphosphate; BB, biomass burning; BC, black carbon; BFHX, bufei huoxue; Br, bromine; Ca, calcium; CH_4, methane; CI, confidential interval; Cl, chloride; CO, carbon monoxide; CO_2, carbon dioxide; COPD, chronic obstructive pulmonary disease; Cr, chromium; Cu, copper; DAQ, data acquisition; DNA, deoxyribonucleic Acid; e-cig, electronic cigarettes; EC, elemental carbon; EMT, epithelial mesenchymal transition; Fe, iron; HC, hydrocarbon; FEV_1, forced expiratory volume in one second; GEF H1, guanine nucleotide exchange factor H1; HPLC FLD, high performance liquid chromatography with fluorescence detection; HRV, heart rate variability; IL, interleukin; K, potassium; KGF, keratinocyte growth factor; LAX, los angeles international airport; Mel, melatonin; Mg, magnesium; miRNA, mitochondrial ribonucleic Acid; Mn, manganese; MT, microtubule; mTOR, mammalian target of rapamycin; Na, sodium; Ni, nickel; NO_x, nitrogen oxides; O_3, ozone; OC, organic carbon; OFP, ozone formation potential; P, phosphorus; P, probability; PAHs, polycyclic aromatic hydrocarbons; Pb, Lead; PEFR, peak expiratory flow rate, $PM_{2.5}$, particulate matter with diameter of>1.0-2.5micrometers (fine PM); PM_{10}/PM_{COARSE}, particulate matter with diameter of>2.5-10.0micrometers (coarse PM); PMN, polymorphonuclear leukocyte; ROS, reactive oxygen species; RR, relative risk; S, sulfur; sIgA, secretory immunoglobulin A; SO_2, sulphur dioxide; STEMI ST, segment elevation myocardial infarction; Ti, titanium; TLR, toll liked receptor; US, united states; VCAM 1, vascular cell adhesion molecule 1; WHO, world health organization; WIS, water insoluble; Zn, zinc.

Introduction

Biomass burning (BB) is of global concern, especially in recent years due to its association with climate change.[1] In China, BB, an observational role in unexpected severe haze episodes overlapped with the primary and secondary pollutants that are derived from coal combustion and engine exhausts.[1] Emissions of significant amounts of greenhouse gases, such as nitrogen oxides (NO_x), sulphur dioxide

(SO_2), and smoke particles with carrying carcinogenic substances from agricultural residues burning calls for close attention.[1] BB also emits significant amounts of short-living global warming substances, such as black carbon (BC),[1] carbon monoxide (CO), carbon dioxide (CO_2), methane (CH_4), volatile organic compounds (VOCs), semi-VOCs, aldehyde, organic acids, inorganic elements, and particulate matter (PM).[2] From observation in at a rural site in Northern China during summer 2013, a significant amount of propene (active VOCs), ozone (O_3) precursors, isoprene, and toluene have been detected with high total O_3 formation potential (OFP) values.[1] VOCs and NO_x can contribute to O_3 formation by photochemical reactions.[1] In China, polycyclic aromatic hydrocarbons (PAHs), both particulate and gaseous phases are emitted from rice, corn, and wheat straws with emission factors of 5.26, 1.74, and 1.37mg/kg, respectively.[1] In 2004, the total PAHs emissions from the burning of three agricultural crop residues in China were approximately 1.09Gg.[1] SO_2 level in the air near a copper smelter in Bor, Serbia from 2009 to 2015 measured at the suburban area (3,734 μg/m^3) was approximately 187 times higher than the limit value determined by the World Health Organization (WHO).[3]

Diesel engine that is being widely use in daily life in both stationary and mobile applications can release harmful gases, such as NO_x, CO, hydrocarbon (HC), and particulate matter into the atmosphere.[4] A recent study on electronic cigarettes (e-cig) demonstrated that small airway epithelial cells exposed to e-cig emission generated up to about eight times more reactive oxygen species (ROS) compared to control group.[5] A previous study reported that e-cig emitted particles that deposited in the head region, including upper respiratory tract could be translocated to the brain via the olfactory bulb.[6] A previous study in eastern Mediterranean during 2011 to 2012 revealed that during cold seasons, regional airflows triggered the accumulation of locally produced $PM_{2.5}$, whereas the impact of dust plumes originated from deserts in northeast Africa, the Middle East, and Syria was apparent on $PM_{2.5}$ and principally on PM_{COARSE} concentrations.[7] Conversely, in warm seasons, weaker dust PM_{COARSE} contributions were detected in Limassol from areas in Libya and Egypt.[7] Elevated particulate-phase PAH concentrations in transportation and technologies of heating in Syria and Turkey, and fire events in central Turkey were possible sources of exogenous PAH warm and cold seasons, respectively.[7] Chemical composition of $PM_{2.5}$ was studied in an urban area of Delhi, India demonstrated that trace elements (sodium (Na), magnesium (Mg), aluminum (Al), phosphorus (P), sulfur (S), chloride (Cl), potassium (K), calcium (Ca), chromium (Cr), titanium (Ti), arsenic (As), bromine (Br), lead (Pb), iron (Fe), zinc (Zn), and manganese (Mn)) was accounted for approximately 22 % of $PM_{2.5}$ mass.[8]

A previous study in Krakow, Poland demonstrated that the mean concentrations of $PM_{1.0}$ and $PM_{2.5}$ were 12+/-5 and 22+/-12 μg/m^3, respectively and the $PM_{2.5}$ fraction contained about 60+/-15 % of submicron particulate matter.[9] A recent study in mice revealed that total-$PM_{2.5}$ (water soluble components and water insoluble components of $PM_{2.5}$ (WS-$PM_{2.5}$, WIS-$PM_{2.5}$) exposure affected metabolites mainly involved in energy metabolism, metabolism of cofactors and vitamins, amino acid metabolism, and protein biosynthesis, whereas WIS-$PM_{2.5}$ exposure mainly perturbed amino acid metabolism and WS-$PM_{2.5}$ exposure involved carbohydrate metabolism and lipid metabolism.[10] In consideration of the reconstructed $PM_{2.5}$ mass, the highest contribution accounted from particulate organic matter (27.5 %) to other components, such as sea salts (17.1%), ammonium sulphate (16.1 %), soil/crustal matter (16.1 %), ammonium nitrate (13.1%), and light absorbing carbon (10.2%).[8] $PM_{2.5}$ sources at the observational site of Delhi demonstrated that fossil fuel burning, biomass burning, industrial emission, and sea salts were accounted for 13.1 %, 12.3 %, 6.3 %, and 4.1 %, respectively.[8] A recent study on aircraft emissions near Los Angeles International Airport (LAX), United States (US) revealed that $PM_{2.5}$ organic carbon (OC) was 36 % at the LAX site, whereas ROS concentrations demonstrated little spatial variability with no statistically significant difference between the averages identified at LAX (24.75+/-4.01μg Zymosan/m^3) and central Los Angeles (27.77+/-20.32μg Zymosan/m^3), indicating similar concentrations of inhalation exposure to redox active species of $PM_{2.5}$.[11] The variability of ROS activity is best explained by elemental-carbon (EC) emitted traffic, the chemical markers of major identified sources and sulfur, a potential tracer of aircraft emissions with statistically significant higher concentrations of sulfur at the LAX site ($p<0.001$, multiple linear regression analysis).[11] Nevertheless, induced health risk of water soluble component of $PM_{2.5}$, ROS was demonstrated in a recent study in China[12]

Through infrequently, deterioration of cabin air quality via contaminant or infectious agent from either mechanical systems or passengers can affect passengers and crews.[13] Increasing all-age all-cause daily number of deaths related to an increase of 10 μg/m^3 in $PM_{2.5}$-short-term exposure ranging between 0.25 % and 2.08 % depending on the geographical area of the study.[14] O_3, NO_2, and CO have been associated with cardiopulmonary hospital admissions, adverse short-term health effects and daily cardiopulmonary morbidity and mortality.[14] O_3 and NO_2 affect mainly respiratory health outcomes, whereas CO influences principally the cardiac system.[14] Similar effects of added heat wave on respiratory hospitalizations in 16 climate zones throughout California, US from May through October 1999-2009 was found.[15] Exposure to PM_{10} has similar identified increases but smaller and more inconsistent effects are reported after exposure to PM_{COARSE} ($PM_{10-2.5}$).[14] A recent study in China reported that $PM_{2.5}$ influenced the risks of cardiovascular hospitalization, particularly with depression among the elderly (>65 years of age) that peaked on lag day 0 (2.92;1.37-4.50) and lag day 5 (3.65;2.09-5.24) and for PM_{10}, the risks peaked on lag day 0 (4.47;2.13-6.85).[16] On lag day 0, these elderly were more sensitive to $PM_{2.5}$ (9.23;5.09-13.53) and PM_{10} (6.35;3.31-9.49).[16] A recent study in China in 2010 revealed that premature deaths attributed to $PM_{2.5}$ countrywide accounted for approximately 1.27 million in total, and 119,167 deaths for adult chronic obstructive pulmonary disease (COPD), 83, 976 deaths for lung cancer, 390,266 deaths for ischemic heart disease, and 670,906 deaths for stroke.[17, 18]

Significant threats to cardiovascular health are related to fetal or perinatal $PM_{2.5}$ exposures.[19] Children under the age of 5 accounted for 3,995 deaths for acute lower respiratory infections.[17] Approximately, half of the premature deaths were from Chinese counties (the Beijing-Tianjin-Hebei region and the North China Plain) with annual average $PM_{2.5}$ concentrations above 63.6μg/m^3, that covered 16.97 % of the Chinese territory.[17] A recent study on early-life exposome and pulmonary function in children of 1,033 mothers from European Human Early-Life Exposome (HELIX) cohort (France, Greece, Norway, Spain, United Kingdom, and Lithuania) revealed that nine postnatal exposures were related to lower % FEV_1:copper (Cu) (p=0.041), ethyl-paraben (p=0.029), five phthalate metabolites (mono-2-ethyl-5-carboxypentyl phthalate [p=0.016], mono-2-ethyl-5-hydroxyhexyl phthalate [p= 0.023], mono-2-ethyl-5-oxohexyl phthalate [p= 0.014]), facility density around schools (p=0.027), and house crowding (p= 0.015).[20] During processing and production of sugarcane, the concentrations of PM_{10} that emitted are high (up to 21.5mg/m^3), which is concerning given that re-suspended particles of ash in the fields and processing plants have been previously demonstrated containing potentially toxic cristobalite that should be

considered as both a potential acute and chronic respiratory health hazard.[21] For considering the association between the urban built environment and remotely sensed $PM_{2.5}$ concentrations, it is necessary to develop a polycentric urban structure to balance high population density and reduction of traffic emissions in downtown areas by simultaneous optimization of road and bus for reduction of traffic emissions.[22] An alternative for urban development "small blocks and narrow roads" may be considered.[22]

Particulate matter with critical involvement in different epigenetic processes like deoxyribonucleic acid (DNA) hypo or hypermethylation and methylation and acetylation of histone code can induce activation of ROS in mitochondria that posses the ability to trigger redox-sensitive signaling mechanisms and can induce irreversibly transgenerational epigenomic changes or inheritance and human health effects,[23] detected by gene-specific and genome-wide methylation.[24] $PM_{2.5}$ organic extracts, particularly in winter in urban environments by combustion reactions and the atmospheric reactions of gaseous pollutants with hydrocarbon resulting in a large number of dispersed DNA-reactive compounds are generally mutagenic that is associated with cancer risk.[25] Ambient air pollutants, cigarette smoke, and some major carcinogens induce angiogenesis that is one of the major mechanisms of neovascularization in air-pollutant-related cardiovascular disorders and cancers, particularly in susceptible populations.[26]

Monitoring of BB by field observation is a practical method to characterize dynamic changes and properties of BB pollutants.[1] Field observations, as the investigations are conducted on-site close to the actual burning that have a definite advantage over laboratory investigations.[1] Nevertheless, deviations between field investigations and laboratory tests, some unfavorable factors, such as random burning process, ultra-low concentration of target components due to atmospheric dilution, inevitable chemical contaminations, and environmental conditions add the challenges to the practical work.[1] Chemical signals or markers (e.g., some non-methane VOCs, galactosan, mannosan, levoglucose, and potassium), specific target particles (e.g., crstal KCl particles, tar ball, and soot), and diagnostic ratios (e.g., ratios of PAHs and some gaseous species, char-EC/soot-EC, OC/EC, and K^+/EC) are usually used to trace BB in the field and assist making source apportionment of BB emissions.[1]

The $PM_{2.5}$ microstation prototyping "ROkidAIR microstation" was developed and implemented in the two cities of Romania. This microstation prototype required the finding of the optimal solutions for the sensors, for examples: airborne particulate measurement sensor, humidity and atmospheric pressure sensors, temperature, data acquisition and automation system, the power system, and all the associated additional components.[27] This $PM_{2.5}$ microstation has main attributes as the following aspects: small dimensions and reduced weight to insure fast development; stand-alone system that does not require an acclimatized container; the compatibility of measurements with reference instrumentation; maintaining of the calibration over long periods of time; diminishing of the electronic equipment malfunctions; implementation of some dynamic response characteristics; managing the system's authorized users database; calibrating, configuring and checking the state of the of transducers and the measurement devices connected to the data acquisition (DAQ) system; checking the state of the communication equipment; checking the availability of the data communication channels; scheduling the measurement, monitoring and communication sessions; collecting, storing, processing and visualization of the values measured or computed by the transducers and the measurement equipment; sending measured and computed values through the communication channels; and generating measurement and status reports.[27] The hardware configuration of the DAQ system was chosen according to : the number of analog signals to be measured from the transducers; the needed precision and scan rate; the number of analog and digital signals to be generated by the system for eventually controlling some equipment; the need for some signals conditioning; the number of digital interfaces needed for connecting the measurement equipment; the characteristics of the communication equipment ' s interfaces; the environment conditions in which the DAQ system will function; the needed flexibility for using the system in various conditions and situations during the microstation lifetime; and the estimations about future system developments and upgrades.[27] LOTOS-EUROS/Dust coupled with reduced-tangent-linearization 4DVar data assimilation, an integrated dust storm forecast system connected with field station network has been developed by China Ministry of Environmental Protection. This system can reflex the aerosol concentrations from local dust emissions and lead to a decrease of parameter dimension from initially 0 (10^4) to 0 (10^2).[28] Recently, a low cost, simplified, and scaleable pneumotachograph with face mask was studied in neonatal mouse for respiratory measurement.[29] This invention revealed a linear response and clean, steady respiratory traces in which sighs and apneas were clearly seen.[29] This methods provide an inexpensive and relative simple approach to develop a pneumotachograph for non-invasive measurements of neonatal respiration with respiratory disorders and enabling the high-throughput of potential chemotherapies.[29] A recent study in the US on economic benefits of reduced maternal exposure to $PM_{2.5}$ for prevention of preterm birth and development of later-life-cardiopulmonary disorders demonstrated that a simulated countrywide 10 % reduction from 2008 $PM_{2.5}$ concentrations could result in an estimate decrease of 5,016 preterm births and benefits of at least $ 339 million and potentially reaching more than one billion US dollars in the aspect of later-life health effects of preterm birth.[30]

Methods of the study

Search strategy and inclusion criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between 2017 and early 2019. Our first involved performing searches of article abstract/keywords/title using strings of [("$PM_{2.5}$" or "particulate matter $_{2.5}$", " $PM_{2.5}$-related air pollutants", "respiratory and cardiovascular disorders or diseases" or "respiratory and cardiovascular diseases", "novel therapeutics on $PM_{2.5}$ and $PM_{2.5}$-related -induced cardiopulmonary health hazards", "health hazards" or "health impacts", and "economic loss on $PM_{2.5}$ and $PM_{2.5}$-related -induced cardiopulmonary health hazards")]. After a first approach of search, published articles focusing on $PM_{2.5}$ or $PM_{2.5}$-related air pollutants were retained and the information on respiratory and cardiovascular disorders or diseases, novel therapeutics on $PM_{2.5}$ and $PM_{2.5}$-related -induced cardiopulmonary health hazards, health hazards, health impacts, and related economic loss was extracted for having a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round. All keywords combinations from $PM_{2.5}$, $PM_{2.5}$-related air pollutants, respiratory and cardiovascular disorders or diseases, health hazards, and health impacts to bind the population of cases under consideration. Search string for disease groups include ["$PM_{2.5}$" or "$PM_{2.5}$-related air pollutants" or "respiratory and cardiovascular disorders or diseases" or "novel therapeutics on

$PM_{2.5}$ and $PM_{2.5}$-related -induced cardiopulmonary health hazards" or "health hazards" or "health impacts" or "economic loss on $PM_{2.5}$ and $PM_{2.5}$-related -induced cardiopulmonary health hazards"]. The initial literature databases were further manually screened with the following rules:

1) Non-respiratory and cardiovascular disorder/disease-related articles were excluded.

2) Articles that did not report $PM_{2.5}$ or $PM_{2.5}$-related air pollutants related to respiratory and cardiovascular disorders or diseases were not considered, such as commentary articles, or editorial.

3) Non-peer reviewed articles were not considered to be of a scholarly trustworthy validity.

4) Duplicated and non-English articles were removed.

The articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

Result

With strict literature search and screening processes, it yielded 140 articles (early 2019=34 articles; 2018=61 articles; and 2017=45 articles) from 3,968 articles of initial literature database (1952-early 2019). Needed article information was extracted from each article by :

1. Direct information including journal, (research article, review article, meeting abstract, conference abstract, correspondence, author index, editorial board meeting abstract, discussion), book chapter, title, authors, abstract, full text documents of candidate studies, publishing year.
2. Study period.
3. Research (study) method used.
4. Types of air pollutants variables studied.
5. Types of organ system disorder or disease studied.
6. The conclusions made about the health hazards and impacts, novel therapeutics on humans or animal models, and related economic loss. An overview of the information required for the present analysis that was captured by those themes was shown in the Figure 1. Results from 140 yielded articles (Reference number 1 to Reference number 140) was demonstrated in the Figure 1, Table 1 (34 early-2019-published articles), Table 2 (61 2018-published articles) and Table 3 (45 2017-published articles).

Discussion

From this study, the majority of the study focused on $PM_{2.5}$ and $PM_{2.5}$-related air pollutants that induced cardiopulmonary health hazards, compared to impacts on other organ systems (i.e.; dermatological and ophthalmological organ systems), whereas studies of $PM_{2.5}$ and $PM_{2.5}$-related -induced health hazards on neurological, male reproductive organ systems, and fetal and maternal health are gradually growing up in number. There are various pollutants that contribute to a negative impact on human health, particularly cardiopulmonary health hazards.[36]. The main compositions of air pollutants are PM, particularly $PM_{2.5}$ and PM_{10}, O_3, CO, SO_2, and NO_x.[36] Exposure to O_3 is frequently associated with respiratory tract inflammation, whereas exposure to PM, CO, NO_2, and SO_2 is related to pulmonary edema, respiratory and cardiovascular hospitalizations, and cardiopulmonary mortality, including central-nervous-system adverse effects.[36] PM can induce COPD, acute lower respiratory tract illness, lung cancer, ischemic heart disease and can accelerate inflammatory-mediated thrombosis via mitochondrial ROS release, contributing to cardiopulmonary pathologies.[43] PM could alter the expression of inflammatory molecules via complex pathways, such as changes in miRNAs expression and DNA methylation-mediated epigenetic modification.[43] Both *in vitro* and *in vivo* studies reveals that PM induces lung injury and inflammation through endothelial dysfunction.[43] Any compromise to endothelial cells, the key components of lung barrier integrity contributes to vascular leakage and inflammation.[43] Endothelial cells could be the target of PM exposure.[43] Presently, knowledge about PM-induced endothelial cell dysfunction is poor, while interleukin-6 (IL-6) and Rho-mediated disruption of endothelial cell barrier function by PM has been demonstrated.[43]

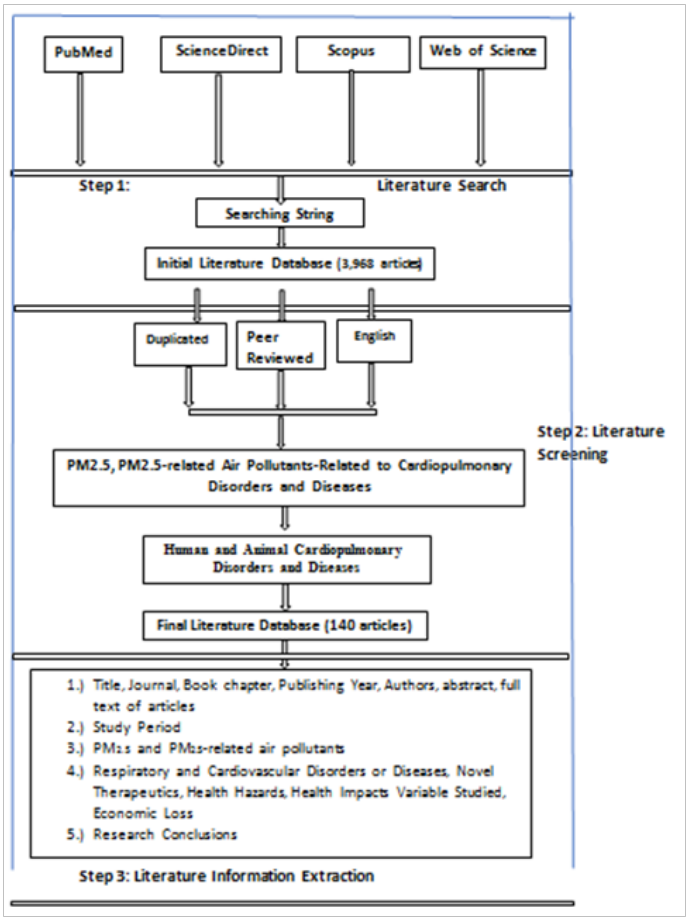

Figure 1 Literature search and screening flow.

MT plays an active role in the regulation of endothelial permeability via cross-talk with actin cytoskeleton, but the role of MT in PM-induced endothelial cell permeability remains unknown.[43] Nevertheless, there are evidences that MT destabilization induced by several agonists impairs endothelial function by the activation of Rho pathway.[43] Combined inhibition of IL-6 and guanine nucleotide exchange factor-H1 (GEF-H1) signaling attenuates PM-induced endothelial cell permeability with additive protective effect.[43] PM exposure has been related to mitochondrial alterations from early life onwards, particularly in children with low mitochondrial DNA.[44] Therefore, any biomarkers of mitochondrial function may assist to identify personal vulnerability of PM exposure.[44] Self-renewal ability

of cells can be achieved via EMT, contributing to airway epithelial remodeling, malignant transformation and pulmonary damage.[48] Nevertheless, the roles of EMT that played in the $PM_{2.5}$-induced lung malignancy remains unclear.[48]

Table 1 Demonstrating 34 early-2019 study results

Published Year	Article Content	Reference
	Concentration measurement, composition of PM2.5 and PM2.5-related air pollutants associated with respiratory, cardiopulmonary and cardiovascular disorders and diseases	12, 13, 22, 31-33
	Health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases (both in human and/or animal models)	20, 23, 34-57
	Novel compounds and drugs in treatment of health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases	58
Early 2019	Economic loss or cost of health impacts due to health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases, including others	30

Table 2 Demonstrating 61 2018-study results

Published Year	Article Content	Reference
2018	Concentration measurement, composition of PM2.5 and PM2.5-related air pollutants associated with respiratory, cardiopulmonary and cardiovascular disorders and diseases	2, 4, 10, 11,,28, 59-65
	Health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases (both in human and/or animal models)	14, 15, 16, 17, 18, 19, 24, 25, 26, 66-103
	Novel compounds and drugs in treatment of health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases	104
	Economic loss or cost of health impacts due to health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases, including others	105

Table 3 Demonstrating 45 2017-study results

Published Year	Article Content	Reference
2017	Types of emissions, concentration measurement, composition of PM2.5 and PM2.5-related air pollutants associated with respiratory, cardiopulmonary and cardiovascular disorders and diseases	3, 4, 6, 7, 8, 9, 27, 106-116
	Health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases (both in human and/or animal models)	1, 21, 117-134
	Modern technologies for low PM2.5 and PM2.5-related air pollutants emissions and novel compounds and drugs in treatment of health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases	135-138
	Economic loss or cost of health impacts due to health hazards associated with PM2.5- and PM2.5-related air pollutants-induced respiratory, cardiopulmonary and cardiovascular disorders and diseases, including others	29, 139-140

Melatonin (Mel), a potent metal chelator and free radical scavenger with strong capacity to reduce ROS/oxidative stress, reduce inflammation, stabilize cell membranes from free radial damage, and protect against sepsis-induced kidney injury.[47] Mel can reduce ischemia-related organ dysfunction mainly via inhibiting inflammation, mitochondrial or DNA damage, the generation of oxidative stress, and cellular apoptosis.[47] Mel acts as a tumor suppressor via interrupting the expression of the senescence-associated secretory phenotype gene.[47] Daily treatment with Mel can protect against endothelial damage, oxidative stress, aging process, and toxic environment in mice.[47] These various effects on various disease entities contribute to hypothesize that Mel might protect the lung integrity against $PM_{2.5}$-induced acute lung injury.[47] YiQiFuMai lyophilized injection can reduce PM-induced acute lung injury in mice through TLR4-mTOR-autophagy pathway,[104] whereas recent study demonstrated that Bufei Huoxue (BFHX) capsules containing three common Chinese herbal products, *Astragalus*, radix paeoniae rubra, and *Psoralea corylifolia*, with approval of the China Food and Drug Administration (Number Z20030063) possibly reduced $PM_{2.5}$-induced pathological responses through the regulation of various inflammatory mediators, including IL-1β, IL-4, IL-6, IL-8, IL-10, and TNF-α in mouse lungs.[137] BFHX could also reduce secretory immunoglobulin A (sIgA) and keratinocyte growth factor (KGF), and collagen fibers deposition in lung, thus, improved pulmonary function.[137]

Most physical exposures, including exposure to PM are strongly associated with degree of urbanization.[33,85] A high land use diversity is consistently related to lower morbidities of particular cardiopulmonary

causes, especially among non-occupationally active persons.[33,85] For considering external costs of PM air pollution in Santiago, Chile, recent study revealed that at peak times, marginal external costs per kilometer for petrol cars, diesel cars, and buses were approximately US$0.51, US$0.53, and US $1.80, respectively.[139] Consideration of all health impacts due to $PM_{2.5}$ pollution in Beijing, China, the economic loss due to premature deaths accounted for over 80 % of the overall external costs.[140]

Conclusion

Due to growing severity and adverse impacts of PM and other air pollutants on human health worldwide, identification of various crucial signaling pathway involving PM-induced cardiopulmonary disorders and diseases may assist in the development of effective therapeutics, including clean energy use, clean industrialization, proper agriculture, high land use diversity, and proper urbanization for reduction of the air pollution.

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None.

Conflicts of interest

Author declares that there is no conflict of interest.

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